IAPP on novel genetic and phenotypic markers of Parkinson's disease and Essential Tremor (MarkMD)
Grant agreement no.: **230596**

SUMMARY OF MARKMD

Project objectives

1. Find genetic markers (CNVs) associated with Parkinson's disease or Essential Tremor (WP1 and WP4)
2. Test genetic markers in patients' cohorts and detailed clinical phenotyping of patients (WP2 and WP4)
3. Test genetic markers in at-risk persons and detailed clinical phenotyping (WP3 and WP4)

Results

WP1

CNVs showing suggestive association in the Icelandic PD sample were tested for association in the larger PD sample from Germany. **Association with CNVs associated with PD prior to MarkMD were confirmed** (unpublished data). deCODE and Tubingen also combined their data in a search for SNPs associating with PD and both groups joined a **large PD meta-analysis**. Through the meta-analysis several genome-wide significant associations were uncovered and results have been published in Lancet [5]. Additional markers could be associated with PD[1-5] and MarkMD partners contributed also to discoveries of markers conferring high-risk of AD[6, 7].
Papers describing pathway analysis [2] of PD markers and heritability estimates derived for PD [3] have been published. The CNV analyses of PD are resulting in a publication.

In particular, the **MarkMD partners focussed on homozygous deletions in the Parking gene**. In a manuscript (being prepared for publication) we show that the heterozygotes carrying a CNV in the Parkin gene are also at risk of PD.

Also, MarkMD establish tools for the detection of uniparental disomy in the deCODE trio cohort in order to detect these potentially phenotype-associated genetic alterations in patients and controls in order to **test the coincidence of segmental uniparental disomy hotspot regions within the human genome with know PD risk loci**.

Furthermore, analysis of **genetic markers in iron genes and BBB genes** was done and the association with iron binding capacity in the Icelandic cohort was tested. Moreover, the elucidate additional genetic markers and complementing the human studies we utilized gene expression datasets of two double-transgenic mouse models of PD overexpressing A30P α-synuclein in combination with Synphilin-1 and with a knockout of Calpastatin, an inhibitor of Calpain).

WP2 and WP3

Detailed clinical phenotyping in Tubingen concentrated on thorough clinical and imaging characterization [11, 12] of patients with Parkinson syndromes. All patients newly recruited were besides the neurological examination including motor scales and transcranial sonography submitted to a non-motor assessment battery including testing for olfaction, mood and cognitive function. In particular, a longitudinal follow up of 93 PD subjects for detection and determination of cognitive impairment was performed. **This knowledge on phenotyping was transferred from Tubingen to deCODE for evaluating high-risk carriers** using a battery of tests overlapping in part with that used in Tubingen. **50 heterozygous Parkin CNV carriers have been carefully phenotyped**. The phenotyping, thus, included a battery of neuropsychological tests, questionnaires for learning difficulties, the MINI interview and MRI for obtaining data on brain structure phenotypes. Brain structure phenotypes and cognitive phenotypes were not associated with a group of control subjects heterozygous for CNVs in the Parkin gene.

WP4

Genotyping as well as CNV and SNP analysis is completed. deCODE and Tubingen associated variants in the LINGO1 gene with ET [10]. **LINGO1 and clinical characteristics of essential tremor ET have been thoroughly investigated** and the role of LINGO1 in the aetiology of ET[8] was further clarified. More particular the effect of the SNP rs9652490 on a range of ET characteristics: sex, age at onset, presence or absence of family history and head tremor, response to propranolol medication and alcohol, and the outcome of finger-nose and spirography tests (Archimedes spirals) was studied.

Tuebingen put a particular focus on the **assessment of ET/PD** through a particular assessment battery. The clinical characterisation of 70-100 patients with ET/PD in Tübingen was carried out including (i) Medical History (PD-specific, ET-specific (OH-response), medication, family history, premotor symptoms, epidemiological data), (ii) Assessments (complete neurological: PD: UK-PDBrainBankCriteria, new UPDRS; ET: Tremor assessment (Fahn Tremor Rating Scale (FTRS); standardized video; Premotor: Sniffin-Sticks, MoCA-Test/Mini-Mental-Status-Test, BDI, Parkinson's Disease Sleep Scale (PDSS), RBD – Questionnair, QoL, ADL, TCS) and (iii) Bloods (DNA, Serum). A first clinical manuscript on ET/PD is in preparation.

Through a transfer of knowledge a more **detailed phenotyping of Islandic ET patients** could be carried out to see, whether a specific genetic marker on chromosome 3 is associated with a specific subgroup. Similar to previously published data slight association of this SNP and the phenotypic subgroup of ET plus writers cramp was found. Few subjects with ET have been MRI scanned at deCODE mainly since subjects carrying high-risk variants are very few and power in the analysis is therefore sparse.

In early summer 2010 MarkMD organized a **European ET meeting** where several groups from all over Europe and the US were invited. Through this effort, collaboration with a group from Kiel was initiated.

Main results achieved

1. Foltynie, T., et al., A genome wide linkage disequilibrium screen in Parkinson's disease. J Neurol, 2005. 252(5): p. 597-602.
2. Holmans, P., et al., A pathway-based analysis provides additional support for an immune-related genetic susceptibility to Parkinson's disease. Hum Mol Genet, 2012.
3. Keller, M.F., et al., Using genome-wide complex trait analysis to quantify 'missing heritability' in Parkinson's disease. Hum Mol Genet, 2012. 21(22): p. 4996-5009.
4. Lill, C.M., et al., Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: The PDGene database. PLoS Genet, 2012. 8(3): p. e1002548.
5. Nalls, M.A., et al., Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet, 2011. 377(9766): p. 641-9.
6. Jonsson, T., et al., A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature, 2012. 488(7409): p. 96-9.
7. Jonsson, T., et al., Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med, 2013. 368(2): p. 107-16.
8. Petursson, H., LINGO1 and clinical characteristics of essential tremor. Masters theses, University of Iceland, 2012.
9. Holmans, P., et al., A pathway-based analysis provides additional support for an immune-related genetic susceptibility to Parkinson's disease. Hum Mol Genet, 2013. 22(5): p. 1039-49.
10. Stefansson, H., et al., Variant in the sequence of the LINGO1 gene confers risk of essential tremor. Nat Genet, 2009. 41(3): p. 277-9.
11. Srulijes K et al. Fluorodeoxyglucose positron emission tomography in Richardson's syndrome and progressive supranuclear palsy-parkinsonism.Mov Disord. 2012 Jan;27(1):151-5..
12. Liscic RM et al. Differentiation of Progressive Supranuclear Palsy: clinical, imaging and laboratory tools. Acta Neurol Scand. 2013 May;127(5):362-70.

Final results and their potential impact

MarkMD succeeded to build a lasting collaboration between leading research organisations with complementory expertise and resources. New projects have been jointly applied for and been awarded such as NeurOmics (www.rd-neuromics.eu).

Contact details

Dr. Holm Graessner, holm.graessner@med.uni-tuebingen.de, +49 7071 2985944

Project web site

www.markmd.eu